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Small Ruminant Lentiviruses: Maedi-Visna & Caprine Arthritis and Encephalitis

*Ovine Progressive Pneumonia,
Marsh's Progressive Pneumonia,
Montana Progressive Pneumonia,
Chronic Progressive Pneumonia,
Zwoegersiekte,
La Bouhite,
Graff-Reinet Disease*

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Importance

Maedi-visna and caprine arthritis and encephalitis are economically important viral diseases that affect sheep and goats. These diseases are caused by a group of lentiviruses called the small ruminant lentiviruses (SRLVs). SRLVs include maedi-visna virus (MVV), which mainly occurs in sheep, and caprine arthritis encephalitis virus (CAEV), mainly found in goats, as well as other SRLV variants and recombinant viruses. The causative viruses infect their hosts for life, most often subclinically; however, some animals develop one of several progressive, untreatable disease syndromes. The major syndromes in sheep are dyspnea (maedi) or neurological signs (visna), which are both eventually fatal. Adult goats generally develop chronic progressive arthritis, while encephalomyelitis is seen in kids. Other syndromes (e.g., outbreaks of arthritis in sheep) are also reported occasionally, and mastitis occurs in both species. Additional economic losses may occur due to marketing and export restrictions, premature culling and/or poor milk production. Economic losses can vary considerably between flocks.

Etiology

Small ruminant lentiviruses (SRLVs) belong to the genus *Lentivirus* in the family *Retroviridae* (subfamily *Orthoretrovirinae*). Two of these viruses have been known for many years: maedi-visna virus (MVV), which mainly causes the diseases maedi and visna in sheep, and caprine arthritis encephalitis virus (CAEV), which primarily causes arthritis and encephalitis in goats. (NB: In North America, maedi-visna and its causative virus have traditionally been called ovine progressive pneumonia and ovine progressive pneumonia virus.) A number of SRLV variants have been recognized in recent decades. As a result, this group of viruses is now classified into five genotypes, A to E. Genotype A is a heterogeneous group, divided into subtypes A1 to A13. It contains the 'classical' maedi-visna viruses and other SRLV variants, including some that infect both sheep and goats. Genotype B (subtypes B1 to B3) contains the classical CAEV strains. The other 3 genotypes, all found in Europe, are less common. Genotype C affects both sheep and goats, while genotypes D and E are divergent goat strains. Recombination can occur between different SRLVs, creating new variants.

Species Affected

SRLVs cause disease in sheep and goats. Classical strains of MVV mainly occur in sheep, but some other genotype A variants infect both species. Genotype C viruses also affect both sheep and goats, while classical CAEV isolates (genotype B), and genotypes D and E mainly occur in goats. The host specificity of SRLVs is not absolute: viruses transmitted from sheep to goats (or vice versa) sometimes adapt to and persist in the new species.

Wild relatives of small ruminants can be infected by SRLVs from domesticated animals. One virus, thought to be CAEV, caused disease in several captive Rocky Mountain goats (*Oreamnos americanus*) that had been fed goat milk as kids, and in another Rocky Mountain goat housed with this group. Mouflon (*Ovis gmelinii*) can be infected experimentally with SRLVs, and genotype B viruses have been detected in wild ibex (*Capra ibex*) in contact with goats. Serological evidence of SRLV infections has also been reported in some species including mouflon, ibex and chamois (*Rupicapra rupicapra*). Preliminary evidence suggests that some viruses in wild ruminants may be distinct from CAEV and MVV.

Other animals are not thought to be hosts for SRLVs. Newborn calves could be infected experimentally with CAEV; however, the infection was asymptomatic and the virus apparently disappeared after 4 months.

Zoonotic potential

There is no evidence that humans are susceptible to any SRLVs.

Geographic Distribution

SRLV genotypes A and B, which contain the classical MVV and CAEV isolates, respectively, are widely distributed. MVV has been found in most sheep-raising countries other than Iceland, where it was introduced but eradicated, and Australia

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and New Zealand. CAEV has been detected in most industrialized countries. Genotypes C (Norway), D (Spain and Switzerland) and E (Italy) appear to be limited to small geographic areas in Europe, at present.

Transmission

MVV and CAEV can be transmitted to lambs, kids or other susceptible species in milk or colostrum. Lactogenic transmission was once thought to be the major route by which SRLVs spread, based on the ability to prevent most infections by removing lambs or kids from their dams at birth. However, this idea has been challenged by some recent studies, and the predominant route is currently unclear. It might differ with the host species, virus and/or management situation. In addition to milk, SRLVs have been found in respiratory secretions and feces, and infections have been demonstrated by intranasal or intraconjunctival inoculation, and via fecally-contaminated water. Most respiratory transmission is thought to occur during close contact; transmission of SRLVs beyond a few meters appears to be inefficient or absent. Coinfection with pulmonary adenomatosis (Jaagsiekte) virus increases contact transmission of MVV between sheep. Feed and water troughs, or the aerosolization of infectious milk in dairies, might be additional sources of virus. Iatrogenic spread through the reuse of needles or other objects that contact blood and tissues (e.g., tail docking equipment) also seems possible. While SRLVs may be spread on fomites, they cannot survive for more than a few days in the environment, particularly under hot, dry conditions.

SRLVs can be found in semen and the female reproductive tract (e.g., uterus) of both sheep and goats, but they do not appear to directly infect oocytes or sperm. Shedding in semen can be intermittent. Sexual transmission is at least theoretically possible, but it does not seem to be common. Intrauterine infection of the fetus by SRLVs is also thought to be negligible or minor, although one study found evidence for MVV infections in 6% of lambs born by caesarean section. Despite the presence of virus in the reproductive tract, it is possible to harvest uninfected ova or early embryos from dams that are either infected or received contaminated semen, as well as to produce uninfected sheep or goat embryos from infected sires or dams by *in vitro* fertilization if certain precautions are taken (see Al Ahmad et al, 2008; Al Ahmad et al, 2012; Fieni et al, 2012 for details).

Once an animal becomes infected, SRLVs are integrated into leukocyte DNA, and the animal carries the virus for life. Viral burdens vary between individual animals; however, both asymptomatic and symptomatic animals can transmit SRLVs.

Disinfection

Lentiviruses can be destroyed with most common disinfectants including lipid solvents, periodate, phenolic disinfectants, formaldehyde and low pH (pH < 4.2).

Phenolic or quaternary ammonium compounds have been recommended for the disinfection of equipment shared between seropositive and seronegative herds.

Incubation Period

The incubation period for SRLV-associated diseases is highly variable, and usually lasts for months to years. Sheep typically develop the clinical signs of maedi when they are at least 3-4 years of age. Visna seems to appear somewhat sooner, with clinical signs in some sheep as young as 2 years. Significant numbers of animals even younger than this were reported during recent outbreaks in Spain, where neurological signs mainly occurred in 1-2 year old sheep, and some cases were seen in lambs as young as 4-6 months.

CAEV-associated encephalitis usually occurs in kids 2 to 6 months of age, although it has also been reported in younger and older animals. Polyarthritis is generally seen in adult goats, although some cases have been reported in animals as young as 6 months.

Clinical Signs

Most SRLV infections in sheep and goats, including infections with classical MVV and CAEV, are asymptomatic. In animals with clinical signs, the disease can take several forms.

Maedi in sheep

Maedi is the most common form of disease in sheep infected with MVV, and usually occurs in adults. It is characterized by wasting and progressive dyspnea. Fever, bronchial exudates and depression are not usually seen. Maedi is eventually fatal; death results from anoxia or secondary bacterial pneumonia. Genotype C viruses can also cause lung lesions (chronic interstitial pneumonia) in sheep.

Visna in sheep

Visna also occurs in adult sheep. This syndrome was described during outbreaks among MVV-infected sheep in Iceland in the 1950s, but it has been reported only sporadically that time. However, it has been relatively common in a recent focus of infection among sheep and goats in northwestern Spain. Visna usually begins insidiously, with subtle neurological signs such as hindlimb weakness, trembling of the lips or a head tilt, accompanied by loss of condition. The clinical signs gradually progress to ataxia, incoordination, muscle tremors, paresis and paraplegia, usually more prominent in the hindlegs. Other neurological signs, including rare instance of blindness, may also be seen. The clinical course can be as long as a year. Unattended animals usually die of inanition.

Arthritis in sheep

MVV can occasionally cause slowly progressive arthritis with severe lameness in sheep, but this is uncommon. One genotype B virus (CAEV) caused an outbreak characterized by enlargement almost exclusively of the carpal joint. Pain and lameness occurred in a

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minority of the affected sheep. No respiratory signs were noted in this outbreak, although some animals had evidence of interstitial pneumonia at necropsy.

Encephalomyelitis in goats

Encephalomyelitis (progressive paresis) is sometimes seen in goats infected with CAEV. Most cases occur in 2-6 month-old kids, although this syndrome has occasionally been reported in younger or older animals. The initial clinical signs may include lameness, ataxia, hindlimb placement deficits, hypertonia and hyperreflexia. Initially, many kids are bright and alert, and continue to eat and drink normally. The signs gradually worsen to paraparesis, tetraparesis or paralysis. Some affected kids may also appear depressed or exhibit other neurological signs (e.g., head tilt, circling, blindness, torticollis, facial nerve deficits, dysphagia). Variable increases in body temperature have been reported. Affected kids are either euthanized for welfare/ economic reasons or eventually die of secondary causes such as pneumonia or exposure. Although it is rare, some goats have apparently recovered.

Neurological signs are uncommon in adult goats infected with CAEV. These cases are usually characterized initially by minor gait aberrations, lameness and knuckling, which progress to paralysis over weeks to months. The reflexes remain intact. Other signs (e.g., coarse tremors, nystagmus, trismus, salivation, blindness) are occasionally reported. Neurological signs may also be seen in goats infected with classical MVV.

Polyarthritis in goats

Chronic, painful polyarthritis, accompanied by synovitis and bursitis, is the main syndrome in adult goats infected with CAEV. This syndrome can occasionally occur in goats as young as 6 months. Early symptoms include distention of the joint capsule and a variable degree of lameness. The carpal joints are most often affected, but symptoms can also occur in other joints. Although the course of disease is slow, it is always progressive. In late stages, goats may walk with their front legs flexed or become recumbent. Affected animals also lose condition and tend to have coarse, dull coats.

Dyspnea in goats

Occasionally, goats with serological evidence of CAEV infection may develop chronic interstitial pneumonia and progressive dyspnea.

Mastitis in sheep and goats

SRLVs including MVV and CAEV can cause chronic indurative mastitis with a swollen, firm mammary gland and decreased production of normal-appearing milk. In severe cases, goats may produce no milk at parturition. The mammary gland may later soften and milk production may approach normal; milk yield remains low in other animals. There are some reports of decreased milk quality in sheep

and goats due to reduced fat content. Sheep infected with genotype C viruses were also reported to have mastitis.

Other effects in sheep and goats

Some studies, but not others, have reported decreased fertility in SRLV-infected animals and lower birth weights in their offspring. Weight gain may be decreased in young animals, possibly due to lower milk yields from dams with indurative mastitis.

Infections in wild or captive wild species

Descriptions of clinical signs due to SRLVs are uncommon in wild species. Captive Rocky Mountain goats infected with CAEV developed signs of chronic pneumonia and wasting, with neurological signs and /or joint lesions in some animals.

Post Mortem Lesions

Maedi [Click to view images](#)

In sheep with maedi, the lungs are enlarged, abnormally firm and heavy, and fail to collapse when the thoracic cavity is opened. They are typically emphysematous and mottled or uniformly discolored, with pale gray or pale brown areas of consolidation. Mottling may not be obvious in the earliest stages of the disease. Nodules may be found around the smaller airways and blood vessels, and the mediastinal and tracheobronchial lymph nodes are usually enlarged and edematous. Secondary bacterial pneumonia may mask the primary lesions.

Neurological forms

Apart from wasting of the carcass, the gross lesions of visna or the encephalitic form of caprine arthritis and encephalitis are usually limited to the brain and spinal cord. In severe cases, there may be focal, asymmetric, brownish pink areas in the white matter of the brain and spinal cord, as well as on the ventricular surfaces. The meninges may be cloudy and the spinal cord may be swollen. Only microscopic CNS lesions are apparent in some cases of neurological disease.

Arthritis [Click to view images](#)

In goats with polyarthritis due to CAEV, the joint capsule is thickened, with proliferation of the synovial villi. The lesions mainly affect the carpal joints, and to a lesser extent the tarsal joints. The joint capsules, tendon sheaths and bursae may be calcified. In severe cases, there may be severe cartilage destruction, ruptured ligaments and tendons, and periarticular osteophyte formation. Goats with caprine arthritis and encephalitis may also have interstitial pneumonitis.

Similar but milder joint lesions, mainly limited to the carpal joints, were reported in an arthritis outbreak among sheep infected with one genotype B (CAEV) virus.

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Mastitis

In animals with indurative mastitis, the udder is diffusely indurated and the associated lymph nodes may be enlarged.

Diagnostic Tests

Diseases caused by SRLVs can be diagnosed by both virological and serological methods; however, all of the currently available tests have limitations. Some authors have suggested using at least 2 different tests for confirmation. Other sources suggest the combination of a diagnostic test (e.g., serology) and clinical signs, with histological examination of tissues when necessary.

Antibodies to SRLVs are usually diagnosed by various enzyme-linked immunosorbent assays (ELISAs) or agar gel immunodiffusion (AGID) tests, using either serum samples or milk. ELISAs have replaced AGID in many laboratories. A number of serological tests, based on different viruses, are available, and the test used should match the variants circulating in the region. Assays vary in their sensitivity and cross-reactivity for other genotypes, and can miss some viruses. Preliminary evidence from one study suggested that tests might also have different sensitivity in sheep and goats. Confirmatory tests may include immunoblotting (Western blotting) and radio-immunoprecipitation; however, these tests are not available in all laboratories. Animals generally seroconvert months after infection, at an unpredictable interval, and antibody titers can fluctuate and/or become intermittently negative in some animals. An additional complication is the existence of many subclinically infected animals, whose clinical signs may be due to some other cause. Due to these limitations, serology may be of greater value in screening herds than diagnosing clinical cases in individual animals.

Polymerase chain reaction (PCR) assays or virus isolation can also be used for diagnosis. These tests may be particularly useful before the animal seroconverts. SRLVs are usually cell-associated; free virus is rarely found in plasma or other fluids. In living animals, viruses can be detected in leukocytes in blood or milk, and possibly in joint fluid in animals with arthritis. Viral titers are variable and may fluctuate over time. At necropsy, SRLVs can be found in affected tissues, such as lung, mediastinal lymph node and spleen (maedi); brain and spinal cord (visna); choroid plexus, udder or synovial membrane. SRLVs can also be detected in alveolar macrophages collected by post-mortem bronchoalveolar lavage at necropsy. Limitations of diagnosis by PCR include the genetic variability between SRLVs (tests based on one set of primers may miss other viruses), and the low virus load. PCR can be confirmed by other genetic techniques such as nucleic acid sequencing to rule out false positives from the host's own genome. Southern blotting or *in situ* hybridization may be performed in some cases, although these tests are not used routinely. SRLVs are isolated by co-culturing peripheral blood or milk leukocytes from live

animals, or fresh tissues collected at necropsy, with sheep choroid plexus cells (MVV), sheep skin fibroblasts (MVV), goat synovial membrane cells (CAEV) or other appropriate cell lines. Virus isolation is not performed routinely and is not always successful.

Histology of affected tissues, using biopsy or necropsy samples, can help confirm the diagnosis in symptomatic animals.

Treatment

There is no specific treatment for diseases caused by SRLVs. Supportive therapy may be helpful in individual animals, but it cannot stop the progression of disease. Measures that may make animals with arthritis more comfortable include regular foot trimming, the provision of additional bedding material, and the administration of NSAIDs. Antibiotics may be used for secondary bacterial infections in cases of mastitis or pneumonitis. High-quality, readily digestible feed may delay wasting.

Control

Disease reporting

Reporting requirements for SRLVs differ between countries, as well as between states/provinces, depending on the presence of official control programs for MVV and/or CAEV, and other factors. Veterinarians who encounter or suspect a reportable disease should follow their national and/or local guidelines for informing the proper authorities. In the U.S, state reporting guidelines should be consulted for caprine arthritis and encephalitis, or maedi-visna (ovine progressive pneumonia).

Prevention

MVV and CAEV are often introduced into a herd in live animals. Additions to uninfected herds should come from SRLV-negative herds. Other animals should be quarantined and tested before adding them to the herd (however, it is possible for tests to miss some viruses). Uninfected herds should also be kept from contact with untested or seropositive herds. Mixing sheep and goats, or feeding milk or colostrum from one species to another, can lead to the transfer of viruses between species. There are currently no vaccines for SRLVs.

If a herd has been infected, several methods can reduce the prevalence of infection or eliminate the virus from the herd. Once the prevalence of infection is low, clinical signs may not be seen. One approach is to completely depopulate the herd and replace it with uninfected animals. Another is to separate lambs or kids permanently from seropositive dams immediately at birth, and raise these animals on uninfected colostrum and pasteurized milk, milk replacer or milk from uninfected animals. The herd should be tested frequently for SRLVs, and seronegative and seropositive animals should be maintained separately. Any shared equipment should be disinfected before use with seronegative animals. Seropositive sheep and goats should

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eventually be culled. Other control methods (e.g., selective culling of seropositive animals, or early culling of seropositive animals with clinical signs) may also be helpful in reducing disease prevalence in an infected herd. In nationwide eradication programs, quarantines of infected herds aid the final stages of the program.

The discovery of genes associated with increased susceptibility to SRLVs may make it possible to produce disease-resistant flocks by selective breeding. Some authors caution that there may be difficulties due to the heterogeneity and high mutation rates of SRLVs, as well as the possibility that resistance is a polygenic trait. One newer approach to reduce or eradicate MVV from a herd is based on mating ewes to rams carrying genes for resistance, raising the lambs naturally until 7 months of age or older, and removing seronegative lambs to a separate flock at this time (see Leymaster et al, 2015 for details).

Morbidity and Mortality

SRLVs are widely distributed among sheep and goats; however, the prevalence of infection in endemic regions can vary widely, ranging from < 5% to more than 60%. Infections tend to be more common in intensively raised herds or flocks, and in animals housed indoors. CAEV is common among dairy goats in most industrialized countries, and uncommon in meat- or fiber-producing goats. The reason for this disparity is unknown, but possible causes include genetic factors or management practices. CAEV is rarely found in the indigenous breeds of developing nations unless they have had contact with imported goats. Genotype C viruses are most common in goats, although they also regularly infect sheep. Control programs have significantly reduced the incidence of MVV and/or CAEV in some countries (e.g., from 60-80% to 1% among goats infected with CAEV genotype B in Switzerland).

Most MVV and CAEV infections are asymptomatic, and clinical signs are usually not seen in herds with a low prevalence of infection. When MVV is introduced into a new area (e.g., in Iceland in the 1950s), the morbidity and mortality rate may reach 20-30%. Morbidity and mortality have also been high in a recent focus of SRLV-associated neurological disease in sheep and goats in parts of Spain. The mortality rate is usually low in regions where classical MVV is endemic; annual losses rarely exceed 5% in a flock, even when nearly 100% of the flock is infected. Co-infection with Jaagsiekte virus, the retrovirus that causes ovine pulmonary adenocarcinoma, results in more severe symptoms. Once clinical signs appear, diseases caused by SRLVs are progressive. While regression of MVV lesions has been documented under some experimental conditions, this is considered unusual. Dyspnea or neurological syndromes are usually fatal, and most animals with arthritis are eventually culled for welfare and/or economic reasons, or die from secondary

causes. Milk production is estimated to decrease by 10% in herds of goats affected by CAEV.

Genetic factors, including breed, influence the outcome of infection in sheep; some breeds (e.g., Texel, Border Leicester, and Finnish Landrace) seem more likely to become ill, while others (e.g., Columbia, Rambouillet, and Suffolk) are more likely to remain subclinically infected. Genes associated with increased susceptibility to disease have also been identified in sheep. Some SRLV isolates also appear to be less virulent than others.

Internet Resources

The Merck Veterinary Manual

<http://www.merckmanuals.com/vet/index.html>

World Organization for Animal Health (OIE)

<http://www.oie.int>

OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals

<http://www.oie.int/international-standard-setting/terrestrial-manual/access-online/>

OIE Terrestrial Animal Health Code

<http://www.oie.int/international-standard-setting/terrestrial-code/access-online/>

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